Docket No. 17581DIV(AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (PATENT)

In Re Application of:
Old et al

U.S. Patent No. 6,812,240 B1
Serial No: 10/765,418

Issued: Nov. 2, 2004
Filed: Jan. 26, 2004

For: **8-AZAPROSTAGLANDIN CARBONATE AND THIOCARBONATE ANALOGS AS THERAPEUTIC AGENTS**

Certificate
FEB 23 2005
of Correction

Commisioner for Patents
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER RULE 322 (OFFICE MISTAKE)

Dear Sir:

Please correct the above-identified patent as shown on the accompanying Certificate of Correction Form PTO-1050.

These corrections are requested for the following reasons:

IN THE SPECIFICATION:

Column 2, line 42, page 3, line 24; delete "Ophthalinol." and insert in place thereof --Ophthalmol.--

Column 2, line 48 page 3, line 28; delete "PGF2α" and insert in place thereof to --$PGF_{2\alpha}$--

Please send the Certificate to:

Allergan, Inc.
ROBERT J. BARAN (T2-7H)
Intellectual Property Dept.
2525 Dupont Drive
Irvine, CA 92612

Respectfully Submitted,

RJ Baran

Robert J. Baran
Registration No. 25,806

Telephone: 714/246-4669;Telecopier: 714/246-4249
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL WITH SUFFICIENT POSTAGE IN AN ENVELOPE ADDRESSED TO: ATTN: CERTIFICATE OF CORRECTION-NON FEE; COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 ON 2/14/2005 Printed Name of Person Making Deposit: Bonnie Ferguson; Signature of Person Making Deposit; Bonnie Ferguson Date: 2/14/05

PTO/SB/44 (07-03)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. Department of Commerce

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

Patent NO. : 6,812,240 B1

DATED : Nov. 2, 2004

INVENTOR(S) : Old et al

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MAILING ADDRESS OF SENDER:
Robert J. Baran (T2-7H)
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

PATENT NO. 6,812,240B1

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No. of additional copies: 10

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8-AZAPROSTAGLANDIN CARBONATE AND THIOCARBONATE ANALOGS AS THERAPEUTIC AGENTS

RELATED APPLICATION

This patent application is a divisional of application Ser. No. 10/453,818 now U.S. Pat. No. 6,734,201 filed Jun. 2, 2003 which is hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to 8-Azaprostaglandin carbonate and thiocarbonate analogues as therapeutic agents, e.g. for the management of glaucoma.

2. Description of Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

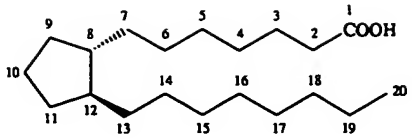
Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the cahal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last decade shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of glaucoma (see, for example, Bito, L. Z. *Biological Protection with Prostaglandins*, Cohen, M. M., ed., Boca Raton, Fla., CRC Press Inc., 1985, pp. 231–252; and Bito, L. Z., *Applied Pharmacology in the Medical Treatment of Glaucomas* Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477–505. Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_2 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

Although the precise mechanism is not yet known experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et.al., *Invest. Ophthalmol. Vis. Sci.* (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more effective penetration through the cornea. In 1987, this compound was described as "the most potent ocular hypotensive agent ever reported" [see, for example, Bito, L. Z., *Arch. Ophthalinol.* 105. 1036 (1987), and Siebold et.al., Prodrug 5 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular PGF2α and its prodrugs, e.g., its 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma are greatly limited by these side effects.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending U.S. Ser. No. 596,430 (filed 10 Oct. 1990, now U.S. Pat. No. 5,446,041), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application U.S. Ser. No. 175,476 (filed 29 Dec. 1993). Similarly, 11,15-9,15 and 9,11-diesters of prostaglandins, for example 11,15-pivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications U.S. Ser. No. 385,645 (filed 7 Jul. 1989, now U.S. Pat. No. 4,994,274), Ser. No.

Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

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